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The stability and Hopf bifurcation analysis of a gene expression model

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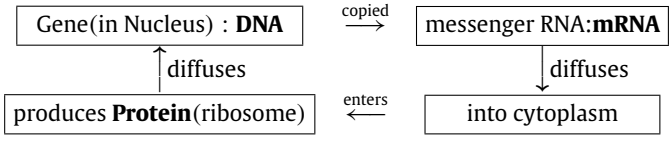
ABSTRACT

In this paper, we investigate a model for gene expression, unlike the models mathematically analyzed previously we have both transcriptional and translational time delays. The stability and Hopf bifurcation of the equilibrium point are investigated. Different to previous papers, a multiple time scale (MTS) technique is employed to calculate the normal form on the center manifold of system of delay differential equations, which is much easier to implement in practice than the conventional method, center manifold reduction. Our results show that when time delay is small the equilibrium is stable, when it is at its critical value Hopf bifurcation happens and while for very large value of time delay the oscillation sustains, which has been confirmed by the published data and proved mathematically by using the global continuity of the Hopf bifurcation in this paper.

1. Introduction

Oscillatory phenomena are commonly encountered in biological problems. This has also been confirmed by experimental data and previous publications [1–5]. Recently, such oscillation has also been observed in a system of gene expression modeling protein Hes1 [2]. This oscillation is particularly important as it is related with the formation of spatial patterns in development [3]. The biology behind the process of gene expression can be illustrated as follows.



From the above chart, mathematical models can be developed. As seen, we have two main precesses here: (a) DNA is copied to messenger RNA (mRNA); (b) Protein diffuses back to nucleus. At the early stage of model development, researchers assume the time for copying the DNA to mRNA is negligible, so is that for the second process, which ends up with a system of ordinary differential equations, see [6,1,2] for instance, which can be proved no sustained oscillation by using the Bendixson's Negative Criterion. It does not agree well with the experimental data, which shows there is a time lag between the protein oscillations and that of mRNA and it is about 20 min under the experimental conditions in [4] for example. Later researchers introduced the transcriptional time delay, which is the time need to copy the DNA to mRNA, to the models which are systems of delay differential equations [7,3,8]. Most recently, Monk introduced a model having both transcriptional time delay and translational time delay, which is the time needed for the protein diffusing back to the nucleus [4]. Most reported

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results so far paid attention to the study of models with the transcriptional time delay only, see [7,3,4,9,10,5], among which Rateitachak investigated a model with a distributed time delay [9], Sturrock investigated a spatio-temporal model, while Verdugo studied a model with discrete time delay by using Lindstedt's method [5]. Most recently, Fu et al. investigated a model with translations time delay by using fourth order Runge–Kutta [11]. To the best of our knowledge, no mathematical investigation has been done on the system modeling the gene expression with two time delays, especially by using multiple time scale technique; there is no mention of the mathematical proof of the existence of the sustained oscillation.

Multiple time scale technique is a global perturbation scheme and has been applied to many weakly nonlinear systems of both ordinary differential equations and partial differential equations, where classical perturbation methods generally break down due to the so-called secular terms [12–14]. Few publications, except Das [15] and Nayfeh [16] apply this method to retarded nonlinear systems.

Since retarded systems or systems of delay differential equations are infinite dimensional, they are generally investigated by a standard procedure, which is known as center manifold reduction [17–20]. The long-term dynamical behavior of the original system of delay differential equations can be caught by that of the normal form on the center manifold near the equilibrium point. The normal form on the center manifold is usually a lower dimensional system of ordinary differential equations, which is relatively easy to investigate. However, the most difficult part in center manifold reduction is the calculation of the normal form, which is a long and tedious procedure. In this paper, we propose to use the concept of multiple scale analysis to compute the normal form on the center manifold near an equilibrium point, which significantly simplifies the whole procedure compared to that of the center manifold reduction.

The mathematical model interested is the one reported by Monk for the first time in [4], where both transcriptional and translational time delays are involved. However, to the best of our knowledge no systematical analysis on this model has been reported in open literatures so far. If τ_m and τ_p denote the transcriptional and translational time delays, respectively and $M(t)$, $P(t)$ denote the concentration of Hes1 mRNA and Hes1 protein, respectively, then we have the model:

$$\begin{cases} \dfrac{dM}{dt} = f(P(t-\tau_m)) - cM(t) \\ \dfrac{dP}{dt} = aM(t-\tau_p) - bP \end{cases} \tag{1}$$

where $f(P) = \frac{\alpha}{1+(P/P_0)^n}.\alpha$ and a are the rate of transcript initiation in the absence of Hes1 protein and the rate at which Hes1 protein is produced from Hes1 mRNA, respectively, P_0 is the reference concentration of protein, n is the Hill coefficient used to characterize binding cooperativity and c and b are degradation rates of Hes1 mRNA and Hes1 protein, respectively. Please also see [4] and the references therein regarding the detailed definition of these parameters appeared in the model. Following Verugo and Rand's idea in [5] we introduce transformation

$$m = \frac{M}{\alpha}, \qquad p = \frac{P}{\alpha a}, \qquad p_0 = \frac{P_0}{\alpha a}$$

to normalize the parameters appeared in model (1). Then it takes the form of

$$\begin{cases} \dfrac{dm}{dt} = \dfrac{1}{1+\left(\frac{p(t-\tau_m)}{p_0}\right)^n} - cm \\ \dfrac{dp}{dt} = m(t-\tau_p) - bp \end{cases} \tag{2}$$

where m, p and p_0 are the normalized concentrations of mRNA and protein and reference concentration of protein.

It is easy to verify that system (2) has unique equilibrium point, (m^*, p^*) determined by

$$\begin{cases} \dfrac{1}{1+\left(\frac{p^*}{p_0}\right)^n} - cm^* = 0 \\ m^* - bp^* = 0. \end{cases} \tag{3}$$

Letting

$$m' = m - m^*, \qquad p' = p - p^*$$

shifts the equilibrium to the origin of the (m', p') plane. For notational simplicity, we will drop the prime in what follows. Then we have the model to be investigated as follows.

$$\begin{cases} \dfrac{dm}{dt} = \dfrac{1}{1+\left(\frac{p_\tau+p^*}{p_0}\right)^n} - c(m+m^*) \\ \dfrac{dp}{dt} = m_\tau - bp. \end{cases} \tag{4}$$

The rest of the paper is organized as follows. Section 2 investigates the linear stability of the equilibrium and also gives the expressions for the critical values of the time delay and natural frequency, ω^*. The normal form on the center manifold shall be calculated in Section 3 by multiple time scale technique and Hopf bifurcation shall be investigated too in this section. In Section 4, we discuss the global continuity of the local Hopf bifurcation. We then conclude this paper in Section 5 with numerical simulations and discussions.

2. Linear stability and boundedness of the solutions of (2)

At the origin, expanding Eq. (4) into Taylor series up to third order gives

$$\dot{X} = NX + N_\tau X_\tau + F \tag{5}$$

where $X = (m, p)^T$, $X_\tau = (m_\tau, p_\tau)^T$ and

$$N = \begin{pmatrix} -c & 0 \\ 0 & -b \end{pmatrix}, \qquad N_\tau = \begin{pmatrix} 0 & -K \\ 1 & 0 \end{pmatrix}, \qquad F = \begin{pmatrix} H_2 p_\tau^2 + H_3 p_\tau^3 \\ 0 \end{pmatrix}$$

with the notations K, H_2 and H_3 defined by [5]. To be self-contained, we list them here

$$K = \frac{n\beta}{p^*(1+\beta)^2}, \quad \text{where} \quad \beta = \left(\frac{p^*}{p_0}\right)^n$$
$$H_2 = \frac{n\beta(n\beta - n + \beta + 1)}{2(1+\beta)^3 p^{*2}}, \quad \text{and}$$
$$H_3 = -\frac{n\beta[(n^2+3n+2)\beta^2 - (4n^2-4)\beta + (n-1)(n-2)]}{6(1+\beta)^4 p^{*3}}.$$

Linearization of Eq. (5) about (0, 0) gives

$$\dot{X} = NX + N_\tau X_\tau \tag{6}$$

which has a characteristic equation

$$\begin{aligned} \Delta &= \lambda^2 + (b+c)\lambda + bc + Ke^{-\lambda(\tau_m + \tau_p)} \\ &\equiv \lambda^2 + (b+c)\lambda + bc + Ke^{-\lambda 2\tau} \end{aligned} \tag{7}$$

where 2τ is the total time delay, and it is easy to see (7) has a pair of pure imaginary roots if and only if there is a positive ω such that

$$-\omega^2 + i(b+c)\omega + bc + K(\cos\omega 2\tau - i\sin\omega 2\tau) = 0 \tag{8}$$

which is equivalent to

$$\begin{cases} -\omega^2 + bc + K\cos\omega 2\tau = 0 \\ (b+c)\omega - K\sin\omega 2\tau = 0. \end{cases} \tag{9}$$

Then, straightforwardly calculating and Rouché's theorem [21] gives the following lemma.

Lemma 1. *For Eq. (7)*

(1) *when $bc > K$, it has no pure imaginary root.*
(2) *when $bc < K$, there is a sequence of values of 2τ:*

$$0 < \tau_0^+ < \tau_1^+ < \cdots < \tau_j^+ < \cdots$$

such that (7) has one pair of pure imaginary roots $\pm i\omega_+$ at $2\tau = \tau_j^+$, and if $2\tau \in [0, \tau_0^+)$ all the roots have negative real parts; if $2\tau = \tau_0^+$ all roots but $\pm i\omega^+$ have negative real parts; if $2\tau \in (\tau_j^+, \tau_{j+1}^+]$ it has $2(j+1)$ roots with positive real parts, where both ω_+ and τ_j^+ satisfy Eq. (9) and given by

$$\omega_+^2 = \frac{-(b^2+c^2) + \sqrt{(b^2-c^2)^2 + 4K^2}}{2}$$
$$\tau_j^+ = \frac{1}{\omega_+}\arccos\left(\frac{\omega_+^2 - bc}{K}\right) + \frac{1}{\omega_+} \times 2j\pi, \quad j = 0, 1, \ldots.$$

From Eqs. (7)–(9), the derivative of λ with respect to τ at τ_j^+ is

$$\frac{d\lambda}{d\tau} = \frac{2\lambda K}{(2\lambda + b + c)e^{2\lambda\tau} - 2K\tau}$$

and then we can easily get

$$\mathbf{Re}\left(\left(\frac{d\lambda}{d\tau}\right)^{-1}\right)\Big|_{\tau=\frac{\tau_j^+}{2}} = \frac{1}{2K^2}\sqrt{(b^2-c^2)^2+4K^2} > 0 \tag{10}$$

where $\mathbf{Re}(\cdot)$ denotes the real part of a complex value. Notice the facts that the product of the real parts of $\frac{d\lambda}{d\tau}$ and $(\frac{d\lambda}{d\tau})^{-1}$ is positive and when $\tau = 0$, i.e. without delay all the roots of (7) have negative real parts. Then from Lemma 1 and the results regarding the stability of the equilibrium in [22,17] we have

Theorem 1. *For system (4)*

(1) *when $\tau = 0$, the trivial solution is stable;*
(2) *when $bc > K$, the trivial solution is stable for all $\tau > 0$;*
(3) *when $bc < K$, the equilibrium is stable if $\tau < \tau^*$ and unstable if $\tau > \tau^*$, where $\tau^* = \tau_0^+/2$;*
(4) *system (4) undergoes Hopf bifurcation at the critical values τ^*.*

3. Multiple time scale technique on the computing of the normal form and the direction of Hopf bifurcation

When $2\tau = \tau_j^+$, Hopf bifurcation might happen. Since when $\tau > \tau^*$ the periodic solution bifurcated from the equilibrium point is always unstable and when $\tau = \tau^*$ system (4) has richer dynamic behavior, which can be determined by the subsystem on the center manifold near the equilibrium point. In what follows, we discuss the case of τ near τ^* and $\tau_m = \tau_p$. Unlike the published literatures where center manifold reduction technique is employed, in what follows we shall develop a Multiple Time Scales (MTS) technique to compute the normal of (5). First, let's normalize the time delay by $t = t'\tau$, then for simplicity of notation we drop the prime. Then (5) becomes

$$\dot{X} = \tau NX + \tau N_\tau X_\tau + \tau F \tag{11}$$

where $X = (m, p)^T$, $X_\tau = (m(t-1), p(t-1))^T$.

Now introduce the time scales $T_0 = t$, $T_2 = \epsilon^2 t$ and here ϵ is a nondimensional bookkeeping parameter. Then the derivative with respect to t is transformed into the following form

$$\frac{d}{dt} = \frac{\partial}{\partial T_0} + \epsilon^2\frac{\partial}{\partial T_2} = D_0 + \epsilon^2 D_2. \tag{12}$$

Next, we shall expand our solution to system (5) in terms of ϵ, namely

$$X(t) = X(T_0, T_2) = \sum_{i=1}^{\infty}\epsilon^i X_i(T_0, T_2). \tag{13}$$

Then we have

$$X(t-1) = X(T_0 - 1, T_2 - \epsilon^2) = \sum_{i=1}^{3}\epsilon^i X_i(T_0-1, T_2) - \epsilon^3 D_2 X_1(T_0-1, T_2) + \cdots. \tag{14}$$

Now introduce a perturbation to the time delay by letting $\tau = \tau^* + \epsilon^2\delta$ and substitute Eqs. (12)–(14) into (11). Equating coefficients of like powers of ϵ gives

$$D_0X_1 - \tau^*NX_1 - \tau^*N_\tau X_{1\tau} = 0 \tag{15}$$

$$D_0X_2 - \tau^*NX_2 - \tau^*N_\tau X_{2\tau} = \tau^* H_2 p_1^2(T_0-1)\mathbf{e}_1 \tag{16}$$

$$\begin{aligned} D_0X_3 - \tau^*NX_3 - \tau^*N_\tau X_{3\tau} \;=\; & -D_2X_1 - \tau^*N_\tau D_2X_{1\tau} + \delta(NX_1 + N_\tau X_{1\tau}) \\ & + (2H_2p_1(T_0-1)p_2(T_0-1) + H_3p_1^3(T_0-1))\tau^*\mathbf{e}_1 \end{aligned} \tag{17}$$

where $\mathbf{e}_1$ is the canonical basis. Then the general solution for the homogeneous equation (15) has the following form

$$X_1 = A(T_2)\mathbf{c}e^{i\omega^*\tau^*T_0} + \overline{A}(T_2)\overline{\mathbf{c}}e^{-i\omega^*\tau^*T_0} \tag{18}$$

with the overhead bar stands for the complex conjugate and

$$\mathbf{c} = \begin{pmatrix}(b+i\omega^*)e^{i\omega^*\tau^*}\\ 1\end{pmatrix}.$$

Notice that $p_1^2(T_0-1)=A^2e^{i2\omega^*\tau^*(T_0-1)}+2A\bar{A}+\bar{A}^2e^{-i2\omega^*\tau^*(T_0-1)}$. Eq. (16) has a particular solution

$$X_2=\mathbf{a}A^2e^{i2\omega^*\tau^*T_0}+\mathbf{b}A\bar{A}+\bar{\mathbf{a}}\bar{A}^2e^{-i2\omega^*\tau^*T_0} \tag{19}$$

substituting which into (16) and equating like terms of $e^{i2\omega^*\tau^*T_0}$ we have

$$\mathbf{a}=\begin{pmatrix}(b+i2\omega^*)e^{i2\omega^*\tau^*}\\ 1\end{pmatrix}a_2 \quad \text{with } a_2=\frac{H_2e^{-i2\omega^*\tau^*}}{(b+i2\omega^*)(c+i2\omega^*)e^{i2\omega^*\tau^*}+Ke^{-i2\omega^*\tau^*}}$$

equating like terms of $A\bar{A}$ gives

$$\mathbf{b}=\begin{pmatrix}b\\ 1\end{pmatrix}b_2 \quad \text{with } b_2=\frac{2H_2}{bc+K}.$$

Substitute Eqs. (18) and (19) into (17). It then becomes

$$\begin{aligned}D_0X_3-\tau^*NX_3-\tau^*N_\tau X_{3\tau} &= -(\mathbf{I}+\tau^*N_\tau e^{-i\omega^*\tau^*})\mathbf{c}A'e^{i\omega^*\tau^*T_0}+\delta(N+N_\tau e^{-i\omega^*\tau^*})\mathbf{c}Ae^{i\omega^*\tau^*T_0}\\ &\quad+(2H_2(b_2+a_2)+3H_3)\tau^*A^2\bar{A}e^{-i\omega^*\tau^*}e^{i\omega^*\tau^*T_0}\mathbf{e}_1+cc+NST\end{aligned} \tag{20}$$

where cc and NST stand for the complex conjugate terms and non-secular terms, respectively. As indicated in [16], Eq. (20) has a solution only if a solvability condition is satisfied. To this end, we shall seek a solution of Eq. (20) in the following form

$$X_3(T_0,T_2)=\phi(T_2)e^{i\omega^*\tau^*T_0}+cc \tag{21}$$

and then by Eq. (20) we have

$$\begin{aligned}(\tau^*N+\tau^*N_\tau e^{-i\omega^*\tau^*}-i\omega^*\tau^*\mathbf{I})\phi(T_2) &= (\mathbf{I}+\tau^*N_\tau e^{-i\omega^*\tau^*})\mathbf{c}A'-\delta(N+N_\tau e^{-i\omega^*\tau^*})\mathbf{c}A\\ &\quad-(2H_2(b_2+a_2)+3H_3)\tau^*A^2\bar{A}e^{-i\omega^*\tau^*}\mathbf{e}_1.\end{aligned} \tag{22}$$

The solvability condition implies that we need to seek a vector $\mathbf{d}$ such that the following adjoint homogenous problem is satisfied.

$$(\tau^*N^T+\tau^*N_\tau^Te^{i\omega^*\tau^*}+i\omega^*\tau^*\mathbf{I})\mathbf{d}=0,\ \mathbf{d}=(d_1,d_2)^T \tag{23}$$

from which we have $d_2=(c-i\omega^*)e^{-i\omega^*\tau^*}d_1$ with d_1 an arbitrary constant. To make d_1 unique and also to simplify our calculation later, we pose a condition

$$\bar{\mathbf{d}}^T\cdot(\mathbf{I}+\tau^*N_\tau e^{-i\omega^*\tau^*})\mathbf{c}=1 \tag{24}$$

(superscript T here stands for the transpose of a vector). Then by (24),

$$\bar{d}_1=\frac{e^{-i\omega^*\tau^*}}{(b+c-2\tau^*(\omega^{*2}-bc))+i2\omega^*(1+\tau^*(b+c))}.$$

Then the solvability condition is obtained by taking the inner product of $\bar{\mathbf{d}}^T$ with Eq. (22) as follows.

$$A'=\delta\Gamma_1A+\Gamma_2A^2\bar{A} \tag{25}$$

where

$$\Gamma_1=\bar{\mathbf{d}}^T\cdot(N+N_\tau e^{-i\omega^*\tau^*})\mathbf{c} \tag{26a}$$

$$\Gamma_2=(2H_2(b_2+a_2)+3H_3)\tau^*e^{-i\omega^*\tau^*}\bar{\mathbf{d}}^T\cdot\mathbf{e}_1. \tag{26b}$$

Next, we shall find the normal form on the center manifold near the equilibrium point, which shall be utilized to investigate the Hopf bifurcation. To this end, in (25) let $A=ze^{-i\omega^*\tau^*t}, z=x+iy$. Then we have the normal form in the real coordinates form:

$$x'=-\omega^*\tau^*y+\delta\,(\mathbf{Re}(\Gamma_1)x-\mathbf{Im}(\Gamma_1)y)+(\mathbf{Re}(\Gamma_2)x-\mathbf{Im}(\Gamma_2)y)\,(x^2+y^2) \tag{27a}$$

$$y'=\omega^*\tau^*x+\delta\,(\mathbf{Re}(\Gamma_1)y+\mathbf{Im}(\Gamma_1)x)+(\mathbf{Re}(\Gamma_2)y+\mathbf{Im}(\Gamma_2)x)\,(x^2+y^2) \tag{27b}$$

where $\mathbf{Re}(\Gamma)$ and $\mathbf{Im}(\Gamma)$ represent the real part and imaginary part of Γ, respectively. The polar form can then be obtained by letting $x=\rho\cos\theta, y=\rho\sin\theta$.

$$\rho'=\rho(\delta K_1+K_2\rho^2)+O(|\rho^4|) \tag{28a}$$

$$\theta'=\omega^*\tau^*+O(|\delta,\rho^2|) \tag{28b}$$

where $K_1 = \mathbf{Re}(\Gamma_1)$ and $K_2 = \mathbf{Re}(\Gamma_2)$. Then from the Hopf bifurcation theorem, [23,24] say, we know the sign of K_1K_2 determines the direction of the Hopf bifurcation and the stability of the periodic solution bifurcated from the equilibrium:

- If $K_1K_2 < 0 (> 0)$, the Hopf bifurcation is supercritical (subcritical);
- If $K_1K_2 < 0 (> 0)$, the periodic solution is stable (unstable).

In what follows, we shall give the expressions for $\mathbf{Re}(\Gamma_1)$ and $\mathbf{Re}(\Gamma_2)$ in terms of the original parameters. By Eq. (26) and some elementary algebra, we have

$$\begin{cases} \Gamma_1 = \dfrac{-2\omega^{*2} + i\omega^*(b+c)}{\gamma_1 + i\gamma_2} \\ \Gamma_2 = \dfrac{(2H_2(b_2+a_2) + 3H_3)\tau^* e^{-i2\omega^*\tau^*}}{\gamma_1 + i\gamma_2} \end{cases} \tag{29}$$

where

$$\gamma_1 = b + c - 2\tau^*(\omega^{*2} - bc)$$
$$\gamma_2 = 2\omega^*(1 + \tau^*(b+c))$$

which implies that

$$\mathbf{Re}(\Gamma_1) = \frac{-2\omega^{*2}\gamma_1 + \omega^*(b+c)\gamma_2}{\gamma_1^2 + \gamma_2^2}. \tag{30}$$

Noticing a_2 in (19) is given by

$$a_2 = \frac{H_2(\omega^{*2} - bc - i\omega^*(b+c))(\beta_1 + i\beta_2)}{\beta_1^2 + \beta_2^2}$$

with

$$\beta_1 = (\omega^{*2} - bc)(K + bc - 4\omega^{*2}) - 2\omega^{*2}(b+c)^2$$
$$\beta_2 = \omega^*(b+c)(2\omega^{*2} + bc + K)$$

we have

$$\mathbf{Re}(\Gamma_2) = \frac{\Gamma}{K(\gamma_1^2 + \gamma_2^2)} \tag{31}$$

where

$$\begin{aligned} \Gamma = {} & [(\omega^{*2} - bc)\gamma_1 - \omega^*(b+c)\gamma_2][2\tau^* H_2(b_2 + \mathbf{Re}(a_2)) + 3\tau^* H_3] \\ & + 2\tau^* H_2 \mathbf{Im}(a_2)[(\omega^{*2} - bc)\gamma_2 + \omega^*(b+c)\gamma_1]. \end{aligned}$$

4. Global continuity of the local Hopf bifurcation

In order to demonstrate the global continuity of the Hopf bifurcation, we need to show: (a) the boundedness of the solution of (2); (b) it has no $\tau_m + \tau_p$-periodic solution; (c) the existence of the nonconstant-periodic solution.

Lemma 2. *All periodic solutions of (2) are uniformly bounded.*

Proof. Firstly, it is easy to see that if (2) has a nonconstant periodic solution $(m(t), p(t))$, we have $m(t)p(t) > 0$, which implies that the solution must entirely locate in the first or third quadrant. Secondly, we can easily verify that all solutions of (2) associated with a positive initial value still keep positive. Next, we shall demonstrate that all solutions here are uniformly bounded. Notice that all parameters p_0, b, c and n are positive. Then from the first equation in (2) we have

$$\frac{dm}{dt} < 1 - cm \quad \text{for all } t \geq 0 \tag{32}$$

which implies

$$\limsup_{t\to\infty} m(t) < \frac{1}{c} \tag{33}$$

and there exists positive constant D such that for $\tau = \max\{\tau_m, \tau_p\}$

$$0 < m(t) < D \quad \text{for all } t \geq -\tau. \tag{34}$$

Substituting (34) into the second equation in (2) gives

$$\frac{dp}{dt} < D - bp \quad \text{for all } t \geq 0 \tag{35}$$

which implies

$$\limsup_{t\to\infty} p(t) < \frac{D}{b}. \tag{36}$$

Consequently there exists a constant E such that

$$0 < p(t) < E. \tag{37}$$

In the rest of the proof, we shall show all periodic solution in third quadrant are also uniformly bounded. We then have three cases to prove: (i) $m(t)$ is unbounded; (ii) $p(t)$ is unbounded; (iii) both $m(t)$ and $p(t)$ are unbounded. We shall show none of them are true.

Case (i): There is constant N such that $-N < p(t) < 0$ for all $t > 0$. Since $m(t)$ is unbounded, there exists $T > 0$ such that $m(t) < -\frac{1}{b}N$ for $t > T$. Then from the second equation in (2) we have

$$\frac{dp(t)}{dt} = m_\tau - bp(t) < -\frac{1}{b}N - bp(t) < \left(b - \frac{1}{b}\right)N < 0 \quad \text{for } t > T$$

which conflicts with the fact that $(m(t), p(t))$ is a periodic solution. Similarly, we can prove $\frac{dp(t)}{dt} > 0$, $t > T$ for the case of (ii), which implies that $p(t)$ along cannot be unbounded.

Case (iii): If both $m(t)$ and $p(t)$ are unbounded, then there exist $T > 0$ and $M > 0$ such that when $t > T$, $m(t) < -M$ and $-cM < \frac{1}{1+(p_\tau/p_0)^n} < 0$. Then from the first equation of (2) we have

$$\frac{dm(t)}{dt} = \frac{1}{1+\left(\frac{p_\tau}{p_0}\right)^n} - cm(t) > \frac{1}{1+\left(\frac{p_\tau}{p_0}\right)^n} + cM > 0$$

for $t > T$, which conflicts with the fact that $(m(t), p(t))$ is a periodic solution.

This completes the proof of Lemma 2. □

Since the periods we are interested in here are the multiples of τ_m and τ_p for $p(t)$ and $m(t)$, respectively, next we shall prove (2) has no solution of period 2τ, $2\tau = \tau_m + \tau_p$. Notice if the ratio of τ_m and τ_p is irrational there is no such nonconstant periodic solution with period of 2τ. Then next we consider the case of τ_m/τ_p is rational. Now introduce transformation of $x = m(t - \tau_p)$, $y(t) = p(t)$, $\tau' = 2\tau$. For simplicity of notation, we still use τ instead of τ' in the rest of this section. Then the τ-periodic solution of (2) is the τ-periodic solution of the following system

$$\begin{aligned} \frac{dx}{dt} &= f(y) - cx(t) \equiv P(x, y) \\ \frac{dy}{dt} &= x(t) - by(t) \equiv Q(x, y) \end{aligned} \tag{38}$$

where $f(\cdot) = 1/(1 + (\cdot/p_0)^n)$. Then it is easy to show that the divergence of (38)

$$\frac{\partial P}{\partial x} + \frac{\partial Q}{\partial y} = -b - c < 0 \tag{39}$$

which implies that (38) has no periodic solution. Then we reach the following lemma.

Lemma 3. *System (2) has no 2τ-periodic solution.*

We then have the following theorem on the global Hopf bifurcation.

Theorem 2. *For each $2\tau > \tau_j, j = 1, 2, \ldots$, system (2) has at least j positively periodic solutions, where $\tau_j = \tau_j^+$ is defined in Lemma 1.*

Proof. For notational simplicity and also the convenience of using the results from [25], we rewrite (2) into the following form

$$\dot{x}(t) = F(x_t, \alpha, p) \tag{40}$$

which satisfies the conditions $(A_1) - (A_3)$ in [25], following the notations there, we have

$$(\hat{x}_0, \alpha_0, p_0) = \left(x_0, \tau_j, \frac{2\pi}{\omega^*}\right)$$

and

$$\Delta_{(x_0,\tau,p)}(\lambda) = \lambda^2 + (b+c)\lambda + bc + Ke^{-\lambda 2\tau}.$$

Here x_0 is the equilibrium of (40). Again for notational simplicity, we shall use τ' to replace 2τ here and drop of the $'$ in the rest of the proof. It is easy to verify that $(x_0, \tau_k, \frac{2\pi}{\omega^*}), j = 0, 1, \ldots$ are isolated centers. Then from Lemma 1 and Eq. (10), there exist $\epsilon > 0, \delta > 0$ and a smooth curve $\lambda : (\tau_j - \delta, \tau_j + \delta) \to \mathbb{C}$ such that

$$\Delta(\lambda(\tau)) = 0, \quad \text{if } |\lambda(\tau) - i\omega^*| < \epsilon$$

for all $\tau \in [\tau_j - \delta, \tau_j + \delta]$ and

$$\lambda(\tau_j) = i\omega^*, \qquad \frac{d\mathbf{Re}(\lambda(\tau))}{d\tau}\bigg|_{\tau=\tau_j} > 0.$$

Let

$$\Omega_{\epsilon,p_0} = \{(u,p) : 0 \le u < \epsilon, |p - p_0| < \epsilon\} \quad \text{and} \quad \partial\Omega_{\epsilon,p_0} = \{(0,p) : (0,p) \in \Omega_\epsilon\}.$$

Then for $(\tau, u, p) \in [\tau_j - \delta, \tau_j + \delta] \times \partial\Omega_{\epsilon, \frac{2\pi}{\omega^*}}$, $\Delta_{(x_0,\tau,p)}(u + i2\pi/p) = 0$ if and only if $u = 0, \tau = \tau_j, p = \frac{2\pi}{\omega^*}$, which implies the condition (A_4) in [25] is satisfied. Next introducing a function defined by

$$H^{\pm}(x_0, \tau_j, 2\pi/\omega^*)(u,p) = \Delta_{(x_0,\tau_j\pm\delta,p)}(u + i2\pi/p)$$

yields the crossing number

$$\gamma_1(x_0, \tau_j, 2\pi/\omega^*) = \deg_B\left(H^-(x_0, \tau_j, 2\pi/\omega^*), \partial\Omega_\epsilon, \frac{2\pi}{\omega^*}\right) - \deg_B\left(H^+(x_0, \tau_j, 2\pi/\omega^*), \partial\Omega_\epsilon, \frac{2\pi}{\omega^*}\right) = -1.$$

Thus the connected component $\mathbb{C}(x_0, \tau_j, 2\pi/\omega^*)$ passing through $(x_0, \tau_j, 2\pi/\omega^*)$ in $\sum$ is nonempty and

$$\sum_{(\hat{x},\tau,p)\in\mathbb{C}(x_0,\tau_j,2\pi/\omega^*)} \gamma_1(\hat{x}, \tau, p) < 0$$

which implies $\mathbb{C}(x_0, \tau_j, 2\pi/\omega^*)$ is unbounded. From Lemmas 2 and 3, we know the projection of $\mathbb{C}(x_0, \tau_j, 2\pi/\omega^*)$ onto the x-space is bounded and that onto the τ-space is bounded below. From Lemma 1, we have

$$\frac{2\pi}{\omega^*} < \tau_j.$$

Then we can easily to show that there exists $\tilde{\tau} < \tau_j$ such that the projection of $\mathbb{C}(x_0, \tau_j, 2\pi/\omega^*)$ onto τ-space is $[\tilde{\tau}, \infty) \supset [\tau_j, \infty)$ for each $j \ge 1$. From [25], we know there are at least $j + 1$ periodic solutions for $\tau > \tau_j, j \ge 1$. □

5. Simulations and discussions

In our simulation, the values of parameters are taken from the published experimental and theoretical results, such as [3–5]. The Hill coefficient, $n \in [2, 10]$, the reference protein concentration, $P_0 \in [40, 100]$ and the rates of degradation of mRNA and protein, $\mu \in [0.01, 1]$. In what follows, our simulations are made both from the normalized model (2) and original model (1), where $\alpha = 33$ and $a = 4.5$ are used as in [8].

5.1. Supercritical bifurcation

When $b = c = \mu = 0.03/\min, n = 2, p_0 = 0.4 (P_0 = 59.4)$ the critical value for time delay, $\tau^* = 26.3983$ and the equilibrium is $(m^*, p^*) = (0.1684, 5.6134) ((M^*, P^*) = (5.5573, 883.5898))$. In this case, we notice that the sign of $K_1K_2 < 0$ with $K_2 < 0$ from Fig. 4, which implies a stable periodic solution is bifurcated from the equilibrium and it is supercritical from our analytic discussion in Section 3. To verify this claim numerically, we start our simulation with two initial points with one close to the equilibrium and the other far away from it, (0.16, 5.6) and (2, 6) say. Then in order the Hopf bifurcation happens, we have $\delta > 0$ from Section 3. Therefore we use $\tau_m = \tau_p = \tau = 26.5 > \tau^*$ here. Fig. 1(a) and (b) clearly show the trajectory starting from (2, 6) is approaching a limit cycle as time goes, which implies the limit cycle is stable and can also be seen from Fig. 1(c) which shows both concentration of the *mRNA* and that of the protein oscillate with a constant amplitude eventually. Fig. 1(d) reflects the same phenomena by simulating the original model starting from a point far away the equilibrium (M^*, P^*). All these facts tell us that a stable limit cycle is bifurcated from the equilibrium as the time delay τ passes through its critical value τ^*. And of course the equilibrium is stable when time delay is less than τ^*, and no matter how large is it the trajectory will eventually settle down at the steady state as long as $\tau < \tau^*$, see Fig. 2 where $\tau = 25$.

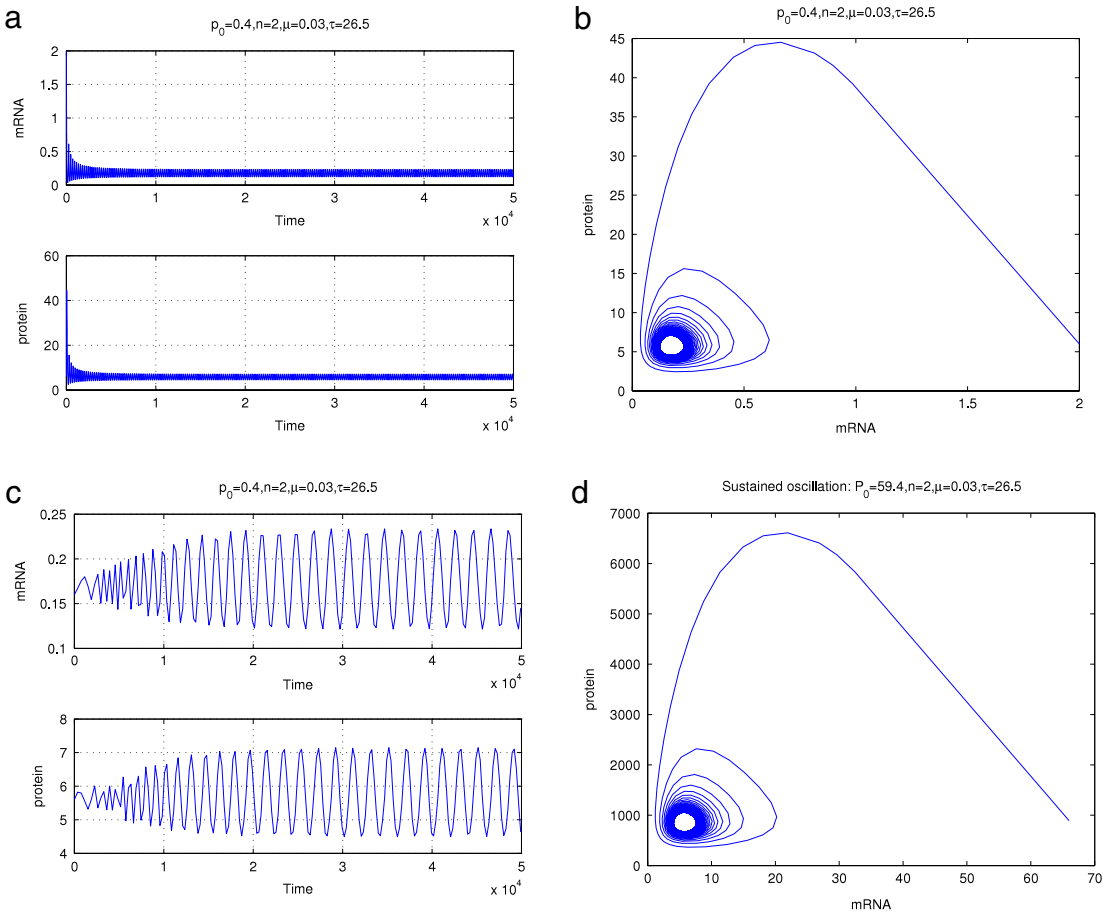
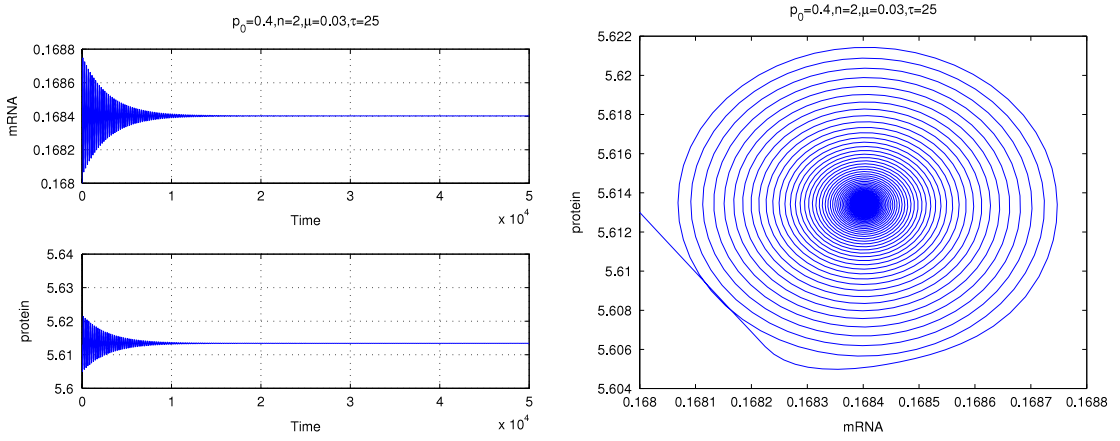


Fig. 1. Phase trajectories for the case of $\tau > \tau^*$ with (a) and (b) starting from (2,6) and (c) starting from initial point at (0.16, 5.6). (a)–(c) from the normalized model and (d) from the original model.



(a) Time vs. mRNA/protein. (b) mRNA vs. protein.

Fig. 2. Phase trajectories for the case of $\tau < \tau^*$ with initial point at (0.16, 5.6).

5.2. Sustained oscillation

To compare with the result from [8], we use $\mu = 0.23$, $n = 2$ and $p_0 = 0.2694$. Then we have $\tau_1^+ = 36.5868$. If the time delay 2τ is much larger than the critical value, say $2\tau = 37$ or even larger, the oscillation will sustain, which is confirmed by the experimental data reported in [8]. Also from our result in Section 4, we have mathematically proved there is a periodic

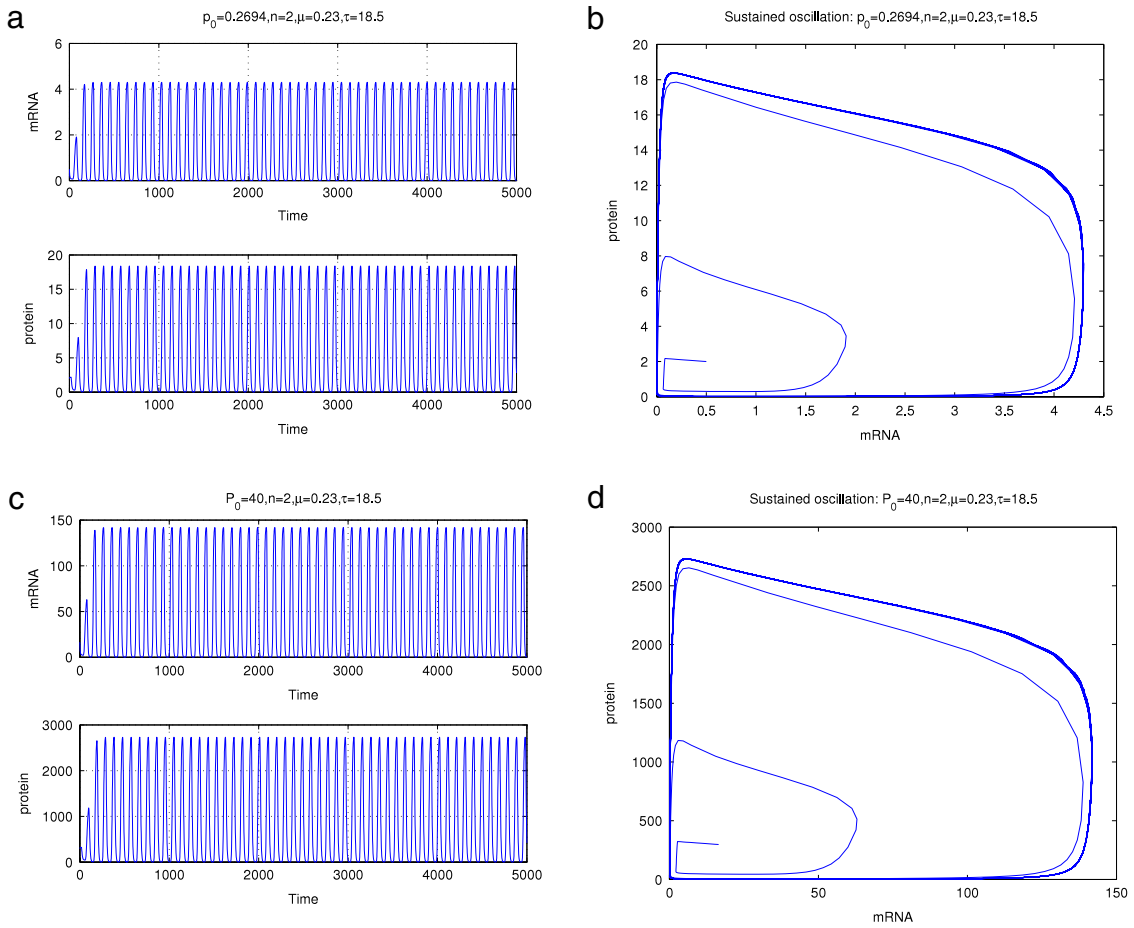


Fig. 3. Sustained oscillation when τ is much greater than its critical value: $\tau > \tau^*$ with initial point at $(m, p) = (0.5, 2)$: (a) and (b) from the normalized model and (c) and (d) from original model.

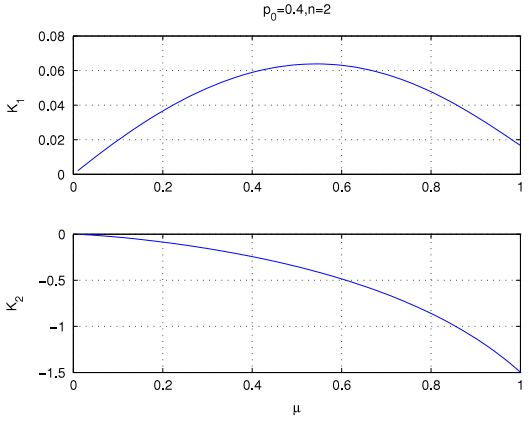


Fig. 4. The bifurcation direction is determined by the sign of K_1K_2.

solution, please see Fig. 3. In this numerical simulation, we use the following values for the time delay, $\tau_m = \tau_p = 18.5$ and initial condition, (0.5, 2) and (16.5, 297) for simulating the normalized model and original mode, respectively. Clearly, a stable limit cycle appears.

5.3. Conclusion

In this paper, we report the investigation of a mathematical model for gene expression, where both transcriptional and translational delays are included. We found the supercritical Hopf bifurcation could happen. Our simulation also shows sustained oscillation happened when the time delay is much greater than its critical value, and we also rigorously prove the existence of the sustained oscillation regarding this model. Different to the conventional methods for delay differential equation, we used multiple time scale technique to calculate the normal form of it on the center manifold near its equilibrium point. As we saw from Section 3, the new method is much easier to implement.

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